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McCune-Albright syndrome in a male child: A clinical and endocrinologic enigma

A 6 5/12-year-old boy with polyostotic fibrous dysplasia, café-au-lait pigmentation of the skin, and precocious pubertal development was studied for two years. Parathormone, calcium, phosphorus, testosterone, cortisol, and growth hormone levels were within normal limits. Urinary 17-ketosteroids, 17-ketogenic steroids, and estrogens were at the upper limits of normal. After GnRH stimulation, there was only a very slight increase in LH and no increase in FSH. There was no increase in TSH after TRH, and plasma levels of T_4 and T_3 were normal. The plasma prolactin level was within normal limits, and increased after TRH stimulation (with a second, delayed upsurge). Abnormal distribution of ^{131}I in the thyroid was evident, without clearcut evidence of hyperfunctioning areas after TSH stimulation and T_3 suppression tests followed by conventional scanning and gamma camera scintiphotography. Our findings do not support the claimed, single, hypothalamic origin of the disease that is presumed to result in overproduction of releasing hormones; they are more in keeping with a pleiotropic, scattered peripheral lesion, possibly of embryonal origin.

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THE ASSOCIATION of polyostotic fibrous dysplasia, café-au-lait pigmentation of the skin, and development of precocious puberty, first mentioned by Weil in 1922,[1] is known as the McCune-Albright syndrome. Since the etiology and pathogenesis of the disorder are still unknown, we report here studies of a 6 5/12-year-old boy. The syndrome occurs predominantly in girls; only ten boys have been reported with precocious puberty.[2] The puberty which occurs in this condition has been referred to as both "true" and "pseudo" precocious puberty by different authors,[15, 16] depending upon the endocrinologic and histologic findings observed in individual cases. As for the pathogenesis, the long-held hypothesis that there is a single, central origin, because of overproduction of hypothalamic-releasing hormones[3] is now in question. More recent evidence suggests that the disorder is of multiple, peripheral origin and that there is autonomous hyperfunctioning of target glands.[4]

There is a well-known association between sexual precocity and other endocrinopathies,[3] particularly adenomatous hyperthyroidism,[5, 10, 13] Cushing disease,[11, 12] and acromegaly.[14]

Abbreviations used

hCG:	human chorion gonadotropin
GH:	growth hormone
GnRH:	gonadotropin-releasing hormone
FSH:	follicle-stimulating hormone
LH:	luteinizing hormone
TRH:	thyroid-releasing hormone
PRL:	prolactin
RIA:	radioimmunoassay
T_3:	tri-idodothyronine
T_4:	thyroxine

CASE REPORT

Patient B. P., a 6 5/12-year-old boy, was referred to the pediatric department because of a hard, painless swelling on the upper medial aspect of the right maxilla. He was the youngest child of a 43-year-old mother who had had four pregnancies. A term male

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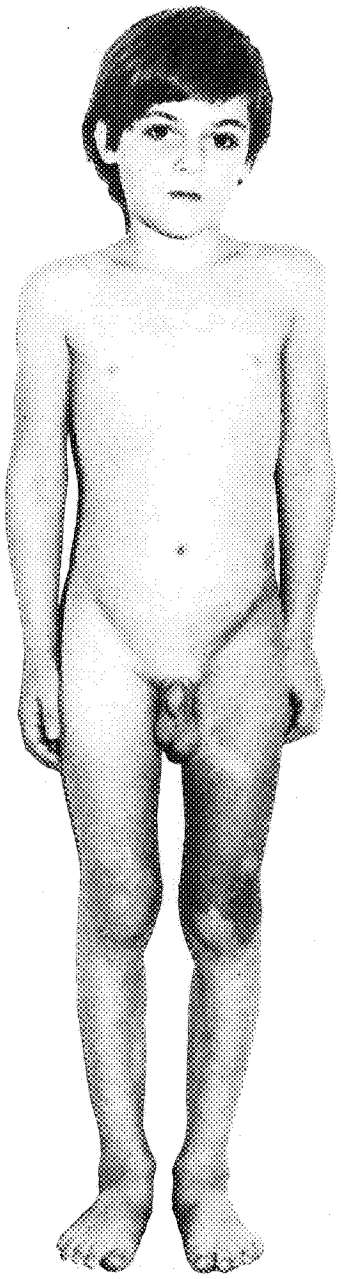


Fig. 1. The patient on admission (6⅝12 years).

infant was born of her first pregnancy; he is now 14 years old and in good health; the second and third pregnancies ended in spontaneous abortions three months (retroversion of the uterus); the fourth pregnancy was term, but there was threatened abortion at 6½ months. The father, a 52-year-old man, had had a right orchiectomy at age 48 for seminoma, that had appeared six years after orchiopexy for cryptorchidism.

The infant weighed 3,800 gm at birth and growth and psychomotor development were normal. When he was one year of age his mother noticed enlargement of both testes, the left being more prominent. Enlargement progressed slowly until age 4 and more rapidly thereafter. The enlargement was always more pronounced on the left side (the mother has been carefully observing the testes because of her husband's previous orchiectomy). A hydrocele was treated with an unknown local method without benefit by the family physician. At age 6, the child developed a painful limp, and after a few months he was referred to us.

Table I. Auxologic data and in vitro thyroid function texts

Data	*Initial and follow-up observations*			
	Admission	*Second*	*Third*	*Fourth*
Age (yr)	6⅝12	6Ⅷ	7⅔12	8Ⅷ
Bone age (yr)*	6	7	8	11
Height (cm)	123.2	126.4	130.8	143
Percentile†	90	90-97	90-97	97
Height-velocity (cm/yr)		10.7		7.9
Testicles (cm³)‡	r = 6 l = 10-12	r = 10-12 l = 15	r = 10-12 l = 15	r = 12 l = 15
Penis-length (cm)	6	6	6	7.5
Pubic hair	P_1	P_1	P_1-P_2	P_2-P_3
T_3 (RIA) (ng/dl)	—	202	204	—
T_4 (RIA) (μg/dl)	—	7.2	—	—
T_4 (D) (μg/dl)	9.2	—	7.9	—
LATS	—	Negative	Negative	—
Antithyroglobulin antibodies	—	—	Negative (TRC) Negative (RIA)	

*According to Greulich and Pyle.
†According to Tanner.
‡Orchidometer of Prader.

The following clinical, growth, and laboratory findings have been gathered in four periods during a period of two years. His general appearance is shown in Fig. 1 (the pigmentation was present at birth, darkened over the next two weeks, then remained unchanged). Growth data are presented in the first column of Table I. Radiologic investigation revealed sclerosis of the base of the skull and of periorbital and facial bones; areas of fibrous dysplasia were scattered throughout the body with rather symmetric distribution; there was widespread but not generalized osteoporosis of variable degree. Growth and sexual development on admission (Table I) showed some contrasting features. The left testis was already adult in size, but the penis was infantile; pubic hair was absent. There was no advancement of bone age.

Biopsy of the left testis revealed large tubular diameters (90 to 170 μ), and scattered areas where all stages of spermatogenesis were visible (Fig. 2); Leydig cells were rare.

At follow-up examination, there was rapid advancement of bone age, presence of a growth spurt, and an increase in the size of both testes. The size of the penis remained unchanged, but a small tuft of straight, thin, slightly pigmented hair was visible at the left base of the penis the time of the third observation (Table

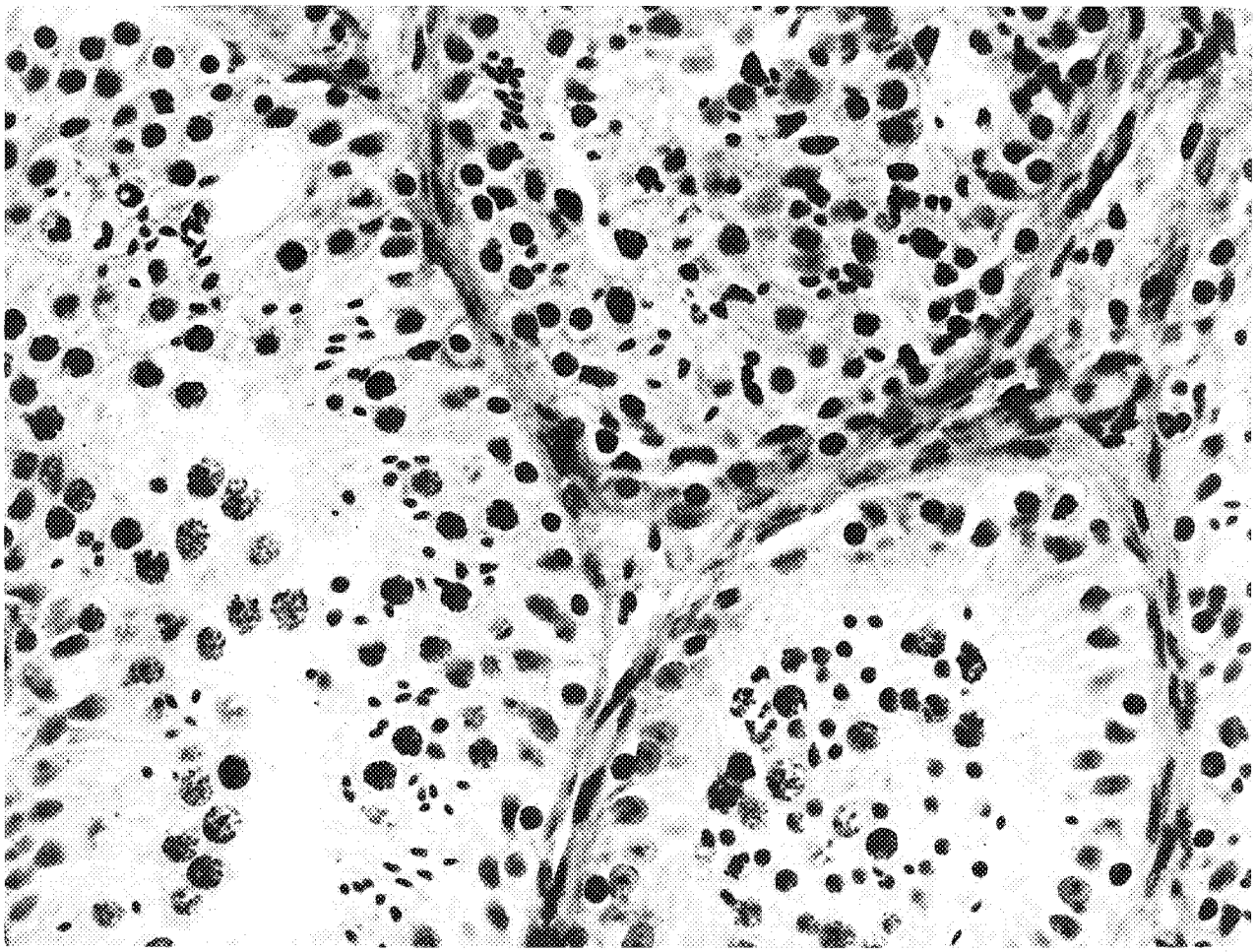


Fig. 2. Mature tubules with evidence of all stages of spermatogenesis.

I). Increased length of the penis was first noticed at the fourth visit.

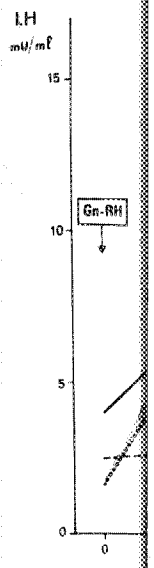
The following studies were within normal limits: complete blood count, blood glucose and urea nitrogen, protein electrophoresis, serum calcium, phosphorus concentrations, urinalysis, urinary excretion of calcium, phosphorus and vanillylmandelic acid. The following were considered to be at the upper limits of normal: estrogens, 11 μg/24 hour (normal values for adult men, 10 to 25 μg/24 hour); 17-ketosteroids, 2.2 mg/24 hours (normal for the age, 0 to 2 mg/24 hours); 17-ketogenic steroids, 3.8 mg/24 hours (normal for the age, 0 to 4 mg/24 hours). Alkaline phosphatase level was slightly elevated for our laboratory standards (10 Bessey-Lowry units). Other endocrinologic investigations revealed the following results: normal parathormone, 8 ng/ml (normal, up to 40 ng/ml); plasma testosterone, before and after stimulation with hCG at high normal prepubertal levels (baseline level, 0.5 ng/ml; peak level after 4 days, 1.40 ng/ml); normal plasma cortisol level (20.8 μg/dl), with increase (Δ = 11.8 μg/dl after 60 minutes) after insulin stimulation and with normal circadian variations (18.2 to 9.3 μg/dl at 8 AM and 4 PM, respectively); normal growth hormone secretion pattern after insulin (baseline level, 1 ng/ml; peak level, 17 ng/ml.)

The secretion of gonadotropins after GnRH stimulation, investigated three times, showed only a slight increase of LH, even under the normal range for prepuberal subjects (Fig. 3). No apparent increase of FSH was demonstrable on any occasion (Fig. 4).

After TRH stimulation test, performed on admission and during the second and fourth visits, there was no increase in the level of TSH or of T_4 or T_3 after 120 minutes (Fig. 5).

Plasma prolactin level rose normally after TRH stimulation (baseline level, 14 ng/ml; peak level, 25 ng/ml).

In vitro thyroid function tests were repeatedly normal (Table I). ^{131}I-uptake test was also normal; moreover, values showed a normal increase after TSH stimulation and a decrease after the T_3 suppression test (Fig. 6). Abnormal distribution of radioactive iodine in the gland was evident on color scanning; TSH stimulation test failed to reveal any dormant area in the right lobe or elsewhere; the incomplete suppression after T_3 directed our attention to the lower part of the left lobe. However, computer-assisted ^{99m}Tc-scintiphotographic investigation, subsequently performed, showed no remarkable prevalence of radioactivity in the lower left lobe and proved more in keeping with a polycentric distribution.



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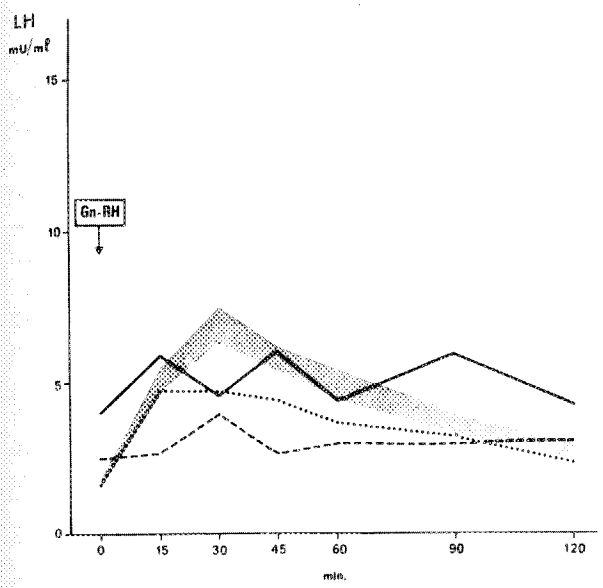

Fig. 3. Luteinizing hormone after intravenous GnRH. Shaded area = normal range for prepuberal children (N = 15); ——— = our patient on admission; ------- second observation; · · · · · · · = fourth observation (see Table I).

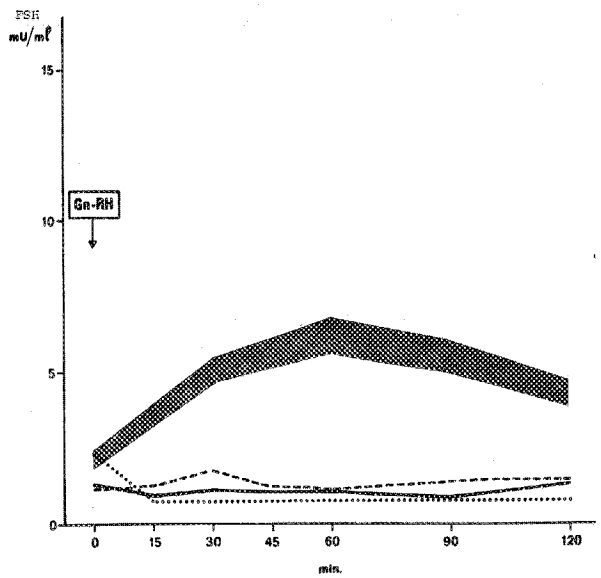

Fig. 4. Follicle-stimulating hormone after intravenous GnRH. Shaded area = normal range for prepuberal children (N = 15); ——— = our patient on admission; ------- second observation; · · · · · · · = fourth observation (see Table I).

METHODS

Human chorionic gonadotropin stimulation test was done with 5,000 U/m² intramuscularly according to the method of Zachmann.[17] Testosterone levels were determined by RIA using a CEA-SORIN kit. By this method both testosterone and dihydrotestosterone are measured. In our laboratory the normal baseline values are 0.24 ± 0.06 ng/ml ($\bar{x}$ ± SEM) in prepuberal children and 0.63 ± 0.14 ng/ml at early puberty (Tanner Stage 2).

An insulin tolerance test was performed with rapid intravenous injection of 0.1 U/kg of regular insulin. Growth hormone was assayed by the double-antibody method.[18] GnRH and TRH tests were done by intravenous injection of 100 and 200 μg/1.73 m², respectively. FSH and LH were determined by RIA with a double-antibody method[19] using SERONO materials.

A similar method[20] with materials of SERONO was used for TSH determination. On one occasion LH, FSH, and TSH were tested simultaneously in our laboratory and in another; the results were almost identical. T_3 (RIA) and T_4 (RIA) were determined using LEPETIT materials.

Plasma PRL levels were determined by RIA using a double-antibody and filtration method (SERONO materials).

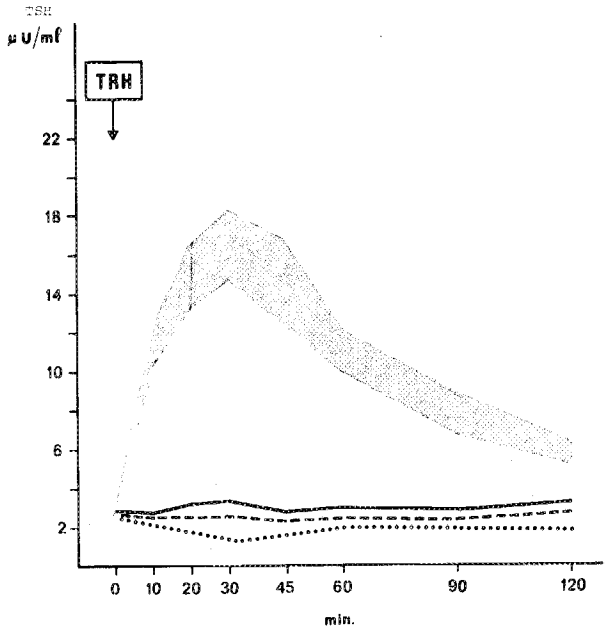

Fig. 5. TSH after intravenous TRH.; ——— our patient on admission;------- = second observation; · · · · · · · = on fourth observation (see Table I). Shaded area = normal range in healthy children (N = 19).

DISCUSSION

The clinical and laboratory studies in our patient revealed the following: (1) the presence of multiple skeletal lesions with no demonstrable impairment of parathyroid function; (2) lack of increase in levels of TSH, FSH, and LH after stimulation with the corresponding hypothalamic-releasing hormones; (3) premature sexual development, which corresponds neither with the pattern

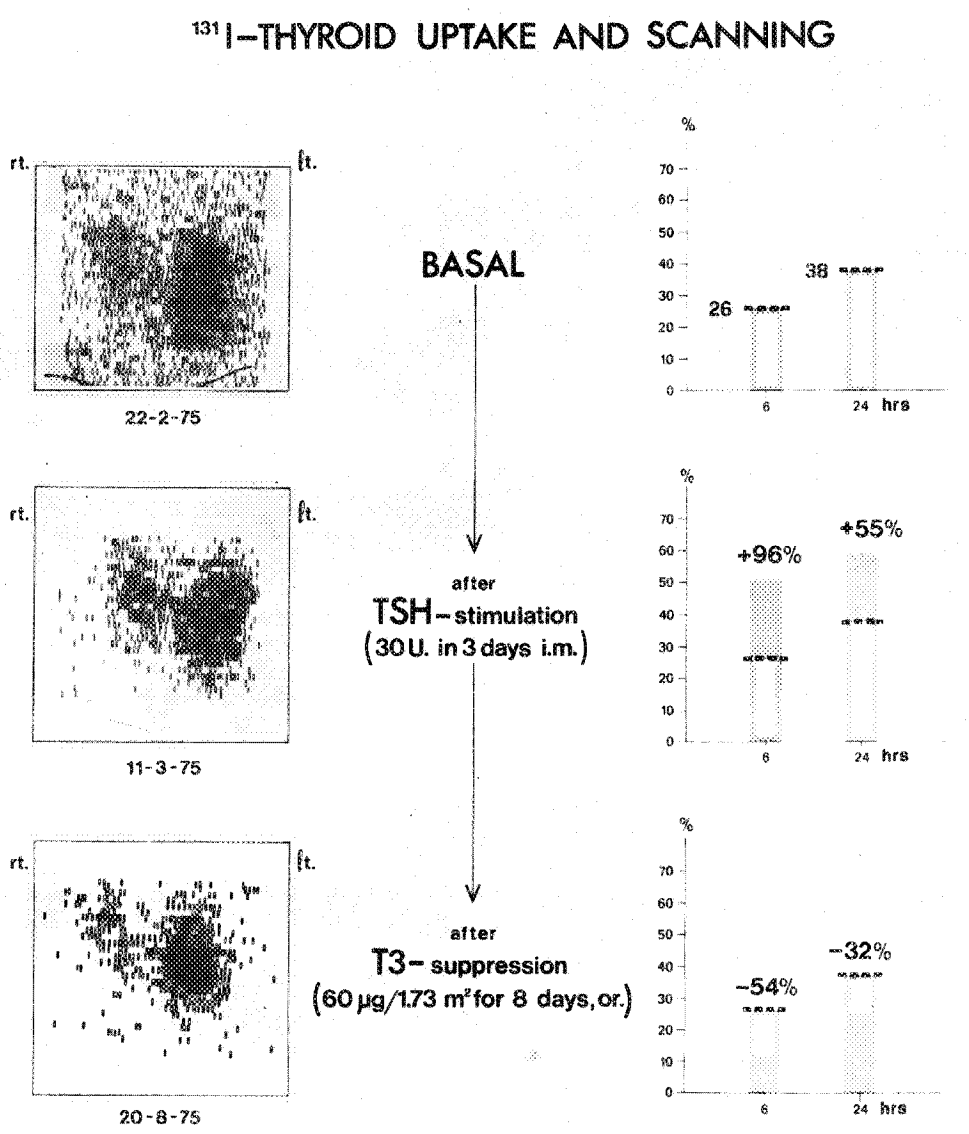

Fig. 6. In vivo thyroid function findings and related behavior after TSH stimulation and T_3 suppression tests.

expected with "true" hypothalamic, nor with "pseudo" precocious puberty. Spermatogenesis was present, even though levels of FSH were low in the basal state and did not increase after GnRH stimulation. Even though the testes were in the adult range of size, penile size was prepubertal, and there was absence of other secondary sexual characteristics and no advancement of bone age (on admission), and (4) abnormal shape of the thyroid gland, in the absence of clinical signs of dysfunction.

A likely explanation for the osseous abnormality is the presence of a congenital abnormal reactivity of clones of cells scattered in the skeletal tissue. The large "silent" area in the right lobe of the thyroid could be explained by a congenital anomaly, perhaps absence of tissue or presence of adenomatous tissue of embryonal type, incapable of ^{131}I uptake. This appears more likely than suppression of thyroid tissue resulting from surrounding hyperfunctioning areas. Failure of increase of TSH after TRH could represent a very early sign of primary, but still subclinical, hyperthyroidism. The unresponsiveness of FSH and, to a lesser degree, of LH to GnRH stimulation could result from pituitary suppression by testicular substances, probably other than testosterone.[21] On the other hand, primary pituitary involvement affecting the beta cells (their overwhelming number and marked pleomorphism having been well documented by Sternberg and Joseph[6] at autopsy of a patient) could constitute an alternative and more encompassing explanation of the observed behavior of the three hormones after stimulation with the corresponding releasing factors.

Although we can draw no definite conclusion about how or where the primary stimulus of the precocious puberty has been triggered in this child, it does not appear that the process is sustained by hypersecretion of gonadotropins. Moreover, the lack of response of gonadotropins to the exogenous releasing hormones is not in keeping with the hypothesis of hypersecretion of hypothalamic-releasing hormones as the cause of the disease.

Our observations do not support the proposed single hypothalamic origin of the disease.[3] A possible explanation in our patient could be primary involvement of some pituitary cell clumps (mainly the beta cells), probably in the context of pleiotropic glandular lesion (see thyroid involvement in our case), which could explain the variable clinical patterns described in this rare syndrome.

CONCLUSION

In spite of the well-known pleomorphism of the clinical and endocrinologic patterns in the McCune-Albright syndrome, the constant feature of the disorder is the scattering of involvement of affected body structures (skeleton, skin, and endocrine glands) which would lead one to hypothesize the presence of multiple, circumscribed embryonic alterations in a variety of tissues, in the form of clones of cells characterized by their aberrant behavior to otherwise normal stimuli.

Recently, the hypothesis has been put forward that the ectodermal and entodermal endocrine glands are related through a common stem cell present in the foregut mucosa, i.e., a multipotential endocrine cell probably of neuroectodermal origin.[9] As is generally admitted, the ectodermal derivatives are the pituitary and adrenal medulla; the entodermal or foregut derivatives are the parathyroid, thyroid, pancreatic islets, and ultimobranchial body.

A congenital dysplasia of some of these stem cells could tentatively explain the origin of the McCune-Albright syndrome, and, as proposed by Weichert,[9] the origin for multiple endocrine adenomatosis. In this connection the remarkable similarity of many aspects of these two syndromes has been discussed in a commentary by DiGeorge.[7]

The association of alterations of bone tissue (mesodermal derivative) with endocrine or neurologic diseases is not rare (this subject has been extensively reviewed by Boenheim and McGavack[22]). Moreover, the polyostotic fibrous dysplasia is also a scattered lesion; the dysplastic areas develop inside the bone; the surrounding cortex and periosteum remain intact; the accompanying osteoporosis is never generalized and may be associated to osteosclerosis; its course is not progressive.[22]

On the whole, our findings and present knowledge seem to be more in keeping with a pleiotropic, scattered peripheral lesion, possibly of embryonal origin, in the McCune-Albright syndrome.

Although new knowledge has been gained, it still may be pertinent to quote from Albright's original paper, "It might be wiser only to describe the condition and not try to come to any conclusion concerning its etiology and the relation of one manifestation to another".[8]

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